INTEGRATED ELECTROPHORETIC MICRODEVICES

FIELD OF THE INVENTION

The field of the invention is electrophoresis.

BACKGROUND

Electrophoresis has become an indispensable tool of the biotechnology and other industries, as it is used extensively in a variety of applications, including the separation, identification and preparation of pure samples of nucleic acids, proteins, carbohydrates, the identification of a particular analyte in a complex mixture, and the like. Of increasing interest in the broader field of electrophoresis is capillary electrophoresis (CE), where particular entities or species are moved through a medium in an electrophoretic chamber of capillary dimensions under the influence of an applied electric field. Benefits of CE include rapid run times, high separation efficiency, small sample volumes, etc. Although CE was originally carried out in capillary tubes, of increasing interest is the practice of using microchannels or trenches of capillary dimension on a planar substrate, known as microchannel electrophoresis (MCE). CE and MCE are increasingly finding use in a number of different applications in both basic research and industrial processes, including analytical, biomedical, pharmaceutical, environmental, molecular, biological, food and clinical applications.

Despite the many advantages of CE and MCE, the potential benefits of these techniques have not yet been fully realized for a variety of reasons. Because of the nature of the electrophoretic chambers employed in CE and MCE, good results are not generally obtainable with samples having analyte concentrations of less than about 10^{-6} M. This lower analyte concentration detection limit has significantly limited the potential applications for CE and MCE. For example, CE and MCE have not found widespread use in clinical applications, where often an analyte of interest is often present in femto- to nanomolar concentration in a complex sample, such as blood or urine.

In order to improve the detection limits of CE, different techniques have been developed, including improved sample injection procedures, such as analyte stacking (Beckers & Ackermans, "The Effect of Sample Stacking for High Performance Capillary Electrophoresis" J. Chromatogr. (1993) 629:371–378), field amplification (Chien & Burgi, "Field Amplified Sample Injection in High-Performance Capillary Electrophoresis," J. Chromatogr. (1991) 559:141–152), and transient isotachophoresis (Stegehuis et al., "Isotachophoresis as an On-Line Concentration Pretreatment Technique in Capillary Electrophoresis," J. Chromatogr. (1991) 538:393–402), as well as improved sample detection procedures and "off-line" sample preparation procedures.

Another technique that has been developed to improve the detection limit achievable with CE has been to employ an analyte preconcentration device that is positioned directly upstream from the capillary, i.e. in an "on-line" or "single flow path" relationship. As used herein, the term "on-line" and "single flow path" are used to refer to the relationship where all of the fluid introduced into the analyte preconcentration component, i.e. the enriched fraction and the remaining waste fraction of the original sample volume, necessarily flows through the main electrophoretic portion of the device, i.e. the capillary tube comprising the separation medium. A review of the various configurations that have been employed is provided in Tomlinson et al, "Enhancement of Concentration Limits of Detection in CE and CE-MS: A Review of On-Line Sample Extraction, Cleanup, Analyte Preconcentration, and Microreactor Technology," J. Cap. Elec. (1995) 2:247–266, and the figures provided therein.

Although this latter approach can provide improved results with regard to analyte detection limits, particularly with respect to the concentration limit of detection, it can have a deleterious impact on other aspects of CE, and thereby reduce the overall achievable performance. For example, analyte peak widths can be broader in on-line or single flow path devices comprising analyte preconcentrators. there is continued interest in the development of improved CE devices capable of providing good results with samples having low concentrations of analyte, particularly analyte concentrations in the femtomolar to nanomolar range.

RELEVANT LITERATURE

MCE devices are disclosed in U.S. Pat. Nos. 5,126,022; 5,296,114; 5,180,480; 5,132,012; and 4,908,112. Other references describing MCE devices include Harrison et al., "Micromachining a Minitiarized Capillary Electrophoresis-Based Chemical Analysis System on a Chip," Science (1992) 261:895; Jacobsen et al., "Precolumn Reactions with Electrophoretic Analysis Integrated on a Microchip," Anal. Chem. (1994) 66:2949; Effenhauser et al., "High-Speed Separation of Antisense Oligonucleotides on a Micromachined Capillary Electrophoresis Device," Anal. Chem. (1994) 66:2949; and Woolley & Mathies, "Ultra-High-Speed DNA Fragment Separations Using Capillary Array Electrophoresis Chips," P.N.A.S. USA (1994) 91:11348.

Patents disclosing devices and methods for the preconcentration of analyte in a sample "on-line" prior to CE include U.S. Pat. Nos. 5,202,010; 5,246,577 and 5,340,452. A review of various methods of analyte preconcentration employed in CE is provided in Tomlinson et al., "Enhancement of Concentration Limits of Detection in CE and CE-MS: A Review of On-Line Sample Extraction, Cleanup, Analyte Preconcentration, and Microreactor Technology," J. Cap. Elec. (1995) 2:247–266.

SUMMARY OF THE INVENTION

Integrated electrophoretic microdevices comprising at least an enrichment channel and a main electrophoretic flow path, as well as methods for their use in electrophoretic applications, are provided. The enrichment channel serves to enrich a particular fraction of a liquid sample for subsequent movement through the main electrophoretic flowpath. In the subject devices, the enrichment channel and electrophoretic flowpath are positioned such that waste fluid from the enrichment channel does not flow through the main electrophoretic flowpath, but instead flows through a discharge outlet. The subject devices find use in a variety of electrophoretic applications where entities are moved through a medium in response to an applied electric field.

BRIEF DESCRIPTION OF THE FIGURES

FIG. **1** provides a diagrammatic view of an enrichment channel for use in a device according to the subject invention;

FIG. **2** provides a diagrammatic view of an alternative embodiment of an enrichment channel also suitable for use in the subject device;

FIG. **3**A provides a top diagrammatic view of a device according to the subject invention;